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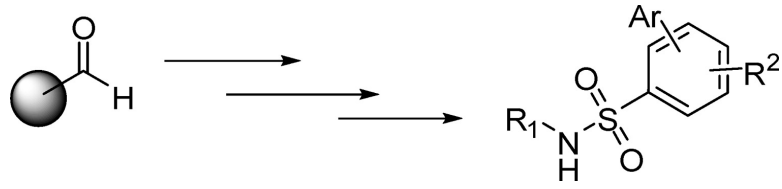

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ClTi(O^{i}Pr)$_3$-Promoted Reductive Amination on the Solid Phase: Combinatorial Synthesis of a Biaryl-Based Sulfonamide Library

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A combinatorial library (9 amines × 7 sulfonyl chlorides × 13 boronic acids = 819 compounds) was produced on solid support in a four-step sequence, i.e., ClTi(O^{i}Pr)$_3$-promoted reductive amination, sulfonylation of the resin-bound amine, Suzuki cross-coupling, and acid-mediated cleavage. The library members were obtained in moderate quantity (1–8 mg) with over 70% of the sampled products greater than 90% pure according to LC-MS analysis.

Introduction

Over the past decade, combinatorial chemistry has been established as a valuable tool for the rapid production of chemical libraries. In drug discovery, the high throughput screening of such libraries, against a variety of biological targets, has been utilized to identify bioactive compounds as chemical starting points for further optimization.[1,2] In connection with ongoing work aimed at the discovery of novel anticancer agents, we became interested in biaryl-based compounds including sulfonamides, as a source of hits against a variety of anticancer targets.[3] This interest stems from the observation that the biaryl core is present in compounds displaying a wide range of biological activities.[4] For example, compound **1** (Figure 1) has been reported as an endothelin-A receptor antagonist,[5] and imatinib (Gleevec), an inhibitor of the BCR-ABL kinase, is currently in clinical use for the treatment of chronic myelogenous leukemia (CML).[6] With this in mind, we set out to produce a compound library (see structure **7** in Scheme 1) based on the biaryl system by combining three monomers: an amine, a substituted sulfonyl chloride, and finally a boronic acid. There are precedents on the solid phase for Suzuki reactions[7,8] and for reductive aminations using alkylamines,[9–11] but the inclusion of anilines and heteroarylamines in this library necessitated the development of novel conditions using a titanium catalyst to promote imine formation.[12]

We decided to follow the split-and-mix approach for the production of this library, in combination with the IRORI-directed sorting technology[13] that could generate a discrete number of compounds in individual microKan reactors, identifiable by electronic tagging.

Results and Discussion

It was envisioned that the biaryl-based sulfonamides **7** could be produced on a solid support in four steps (Scheme 1) utilizing the nitrogen in the sulfonamide bond as the point of attachment to the resin.[14] Reductive amination of the aldehyde **3** with primary amines and subsequent sulfonylation of the resin-bound secondary amine **4** with a bromoarylsulfonyl chloride would give a resin-bound sulfonamide **5**. Suzuki cross-coupling followed by acidic cleavage would afford the desired biaryl-based sulfonamides **7** (Scheme 1).

The conditions for the reductive amination step were first investigated by studying the reaction of the resin-bound aldehyde **3** with 3-amino-5-*tert*-butylisoxazole.[12] The novel TiCl(O^{i}Pr)$_3$/NaBH(OAc)$_3$ system was established as the most efficient reagent combination for this transformation.[12] It was found that in the solution phase, at least 2.2 equiv of TiCl(O^{i}Pr)$_3$ (over the aldehyde) were required for the reaction to go to completion.[12] Similarly, it was found that 1.1 equiv of the amine and at least 2.3 equiv of TiCl(O^{i}Pr)$_3$ were required to perform this reaction on a solid support. This was established by reacting the resin-bound aldehyde **3** with the electron-deficient 2-aminopyrimidine, varying the reaction conditions (Scheme 2, Table 1). Subsequently, the resulting secondary amine **8** was treated with 4-chlorobenzoyl chloride to give the resin-bound amide **9**. Finally, TFA-mediated cleavage afforded the amide **10**, with the highest yield being 63% (Table 1; entries 1 and 2).

Having established a reliable method for the reductive amination of the resin-bound aldehyde **3**, we concentrated on the optimization of step 2, i.e., the sulfonylation of the resin-bound secondary amines **4** (Scheme 1). For this purpose, the secondary amine **11** was synthesized and its reaction with 4-bromobenzenesulfonyl chloride was studied, initially in solution (Scheme 3). A variety of reaction

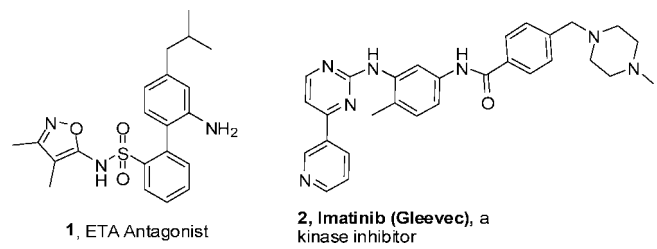

Figure 1

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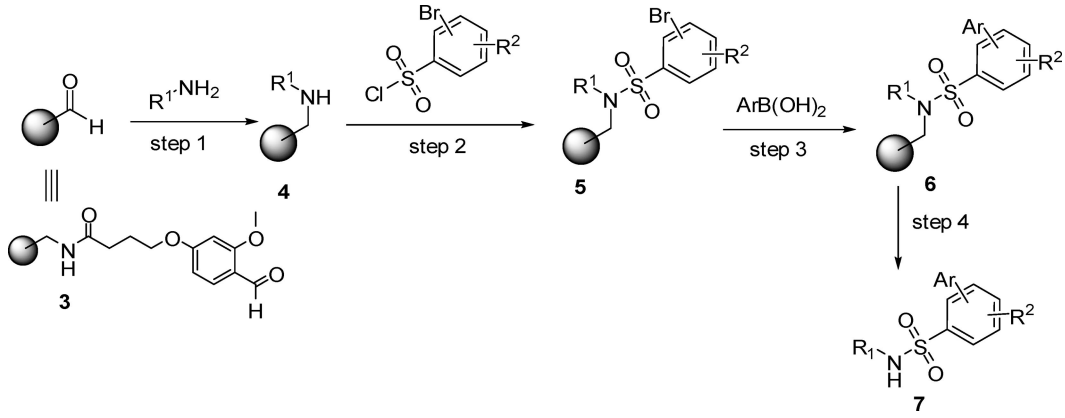
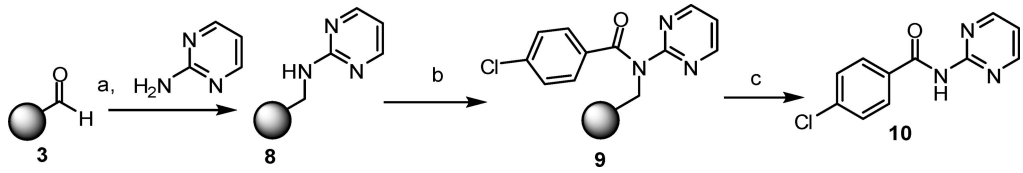
Scheme 1. Solid-Phase Synthesis of Biaryl-Based Sulfonamides



Scheme 2. TiCl(O^iPr)$_3$-Mediated Reductive Amination of Resin-Bound Aldehyde **3**[a]



[a] Conditions: (a) TiCl(O^iPr)$_3$, CH_2CL_2, 20 min, then $NaBH(OAc)_3$, AcOH (cat.), room temperature (rt), 16 h; (b) 4-chlorobenzoyl chloride (10 equiv), ^{i}PrNEt (10 equiv), DMAP, rt, 16 h; (c) 20% TFA/CH_2Cl_2, rt, 1 h.

Table 1. TiCl(O^iPr)$_3$-Mediated Reductive Amination of **3** with 2-Aminopyrimidine

entry	equiv amine	equiv TiCl(O^iPr)$_3$	yield
1	1.1	2.3	63%
2	1.1	4	63% (42%[a])
3	2.0	8	45%
4	1.1	2.3	42%[b]

[a] Isolated yield. [b] The reaction mixture was shaken with TiCl(O^iPr)$_3$ for 7 h before the addition of $NaBH(OAc)_3$.

conditions were explored and it was found that the sulfonylation of **11** proceeds cleanly in chloroform/pyridine (v/v; 4:1) using 4-bromobenzenesulfonyl chloride at a concentration of 0.2 M and DMAP (2 equiv). Subsequently, the analogous sulfonylation reaction was performed in IRORI microKans by applying the solution-phase conditions. On this occasion, two reaction cycles were required to achieve a complete conversion of the resin-bound secondary amine to the corresponding sulfonamide.

In the third step (Scheme 1), the Suzuki cross-coupling reaction of the resin-bound bromosulfonamides **5** with boronic acids was investigated. It was found that, in solution, 3 equiv of the boronic acid in DME (0.5 M) and 3 equiv of Na_2CO_3 (aqueous solution) in the presence of $PdCl_2$(dppf) (10%) at 100 °C drove the reaction to completion. In addition, the reaction worked well in IRORI microKans by a slight modification of the reaction conditions: the reaction time had to be doubled, and a higher concentration of the boronic acid (0.6 M) was required to achieve complete conversion.

Finally, the desired sulfonamides **7** could be obtained from the resin-bound sulfonamides **6** (Scheme 1, step 4) via a TFA-mediated cleavage. For the library production, 50% TFA in CH_2Cl_2 was used to ensure a high yielding cleavage.

A combinatorial library was produced in four steps utilizing the monomers shown in Figure 2 ($9 \times 7 \times 13 = 819$ compounds). It must be noted, though, that the TiCl(O^iPr)$_3$- promoted reductive amination reaction worked less well in IRORI microKans than with loose resin. Therefore, with the reductive amination reaction being the first step in the library production, it was more efficient to perform this transformation on loose resin and then transfer the resin-bound secondary amines into the IRORI microKans for the continuation of library production. To assess the success of the Suzuki cross-coupling reaction, a single Kan was randomly removed from each reaction flask (13 in total), washed, and cleaved. Between 2 and 8 mg of each compound was obtained, and the majority (8 out of the 13 compounds) had a purity of >90% as judged by LC-MS. Based on these results, we proceeded with the last step, i.e. the TFA-mediated cleavage, to isolate the final products. From the entire library, 52 compounds were randomly removed and subjected to LC-MS and ^{1}H NMR analysis. The results from the LC-MS analysis are shown in Table 2 (see the Supporting Information for ^{1}H NMR data).

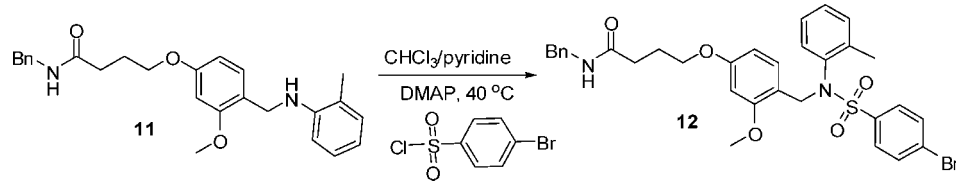
These results show that for 80% of the library members, the purity is >80% and the majority of the compounds (>70%) displayed a purity higher than 90%.

One undesired side product that arose during the library production was the double or triple palladium-catalyzed coupling of 3-chlorobenzene boronic acid. The LC-MS spectra of compounds constructed from 3-chlorobenzeneboronic acid showed bi-, tri- and tetra-aryl compounds. However, ^{1}H NMR quantification showed that these byproducts amounted to no greater than 10% of the cleaved product. It should be noted that $PdCl_2$(dppf) has been shown to be able to insert into Ar−Cl bonds and promote Suzuki-type reaction of aromatic chlorides.[15]

Conclusions

An 819-membered library of biaryl-based sulfonamides was successfully produced in a four-step sequence. The reductive

Scheme 3. Sulfonylation of Secondary Amines



amination step (first step) was initially found to be problematic with heterocyclic amines. This was overcome with the discovery that $TiCl(O^iPr)_3$ greatly facilitated this transformation. Having established a method to attach the heterocyclic amines onto the solid phase, the sulfonylation reaction was optimized, as was the Suzuki cross-coupling reaction. Overall, the library members were obtained in adequate quantity (1–8 mg) and good purity, with over 70% of the sampled products greater than 90% pure according to LC-MS analysis.

Experimental Section—Library Synthesis

General—Library Synthesis. The washing cycles following the reductive amination were performed with 20 mL of each solvent; after the sulfonylation and the Suzuki cross-coupling, 100 mL of each solvent was used. The cycles always began with rinsing the resin or resin-filled Kans with DCM (×2). Each solvent listed was agitated with the resin or resin-filled Kans for 20–30 min before filtering and rinsing the resin or resin-filled Kan with that solvent, except for DMF, which was always rinsed with the following solvent. During each washing, a vacuum (water aspirator) would be applied to the reaction vessel for approximately 1 min and then released; applying a vacuum removes the solvent from the Kans, and when the vacuum is released, the solvent re-enters the Kans. This was done to ensure that the encapsulated resin was being exposed to fresh solvents. Between each solvent wash, the Kans were placed on paper towels and gently patted to remove any remaining solvents.

The washing cycles were as follows:

(A) DCM, MeOH, DCM (×2), Et_2O.

(B) DCM (×2), MeOH, DCM, DMF, MeOH, DMF, MeOH, DCM, MeOH, DCM, MeOH, DCM (×3), Et_2O.

(C) DCM (×2), MeOH, DCM, DMF, DCM, DMF, MeOH, DMF, MeOH, DCM, MeOH, DCM, MeOH, DCM, MeOH, DCM (×3), Et_2O.

(D) MeOH, DCM (×2).

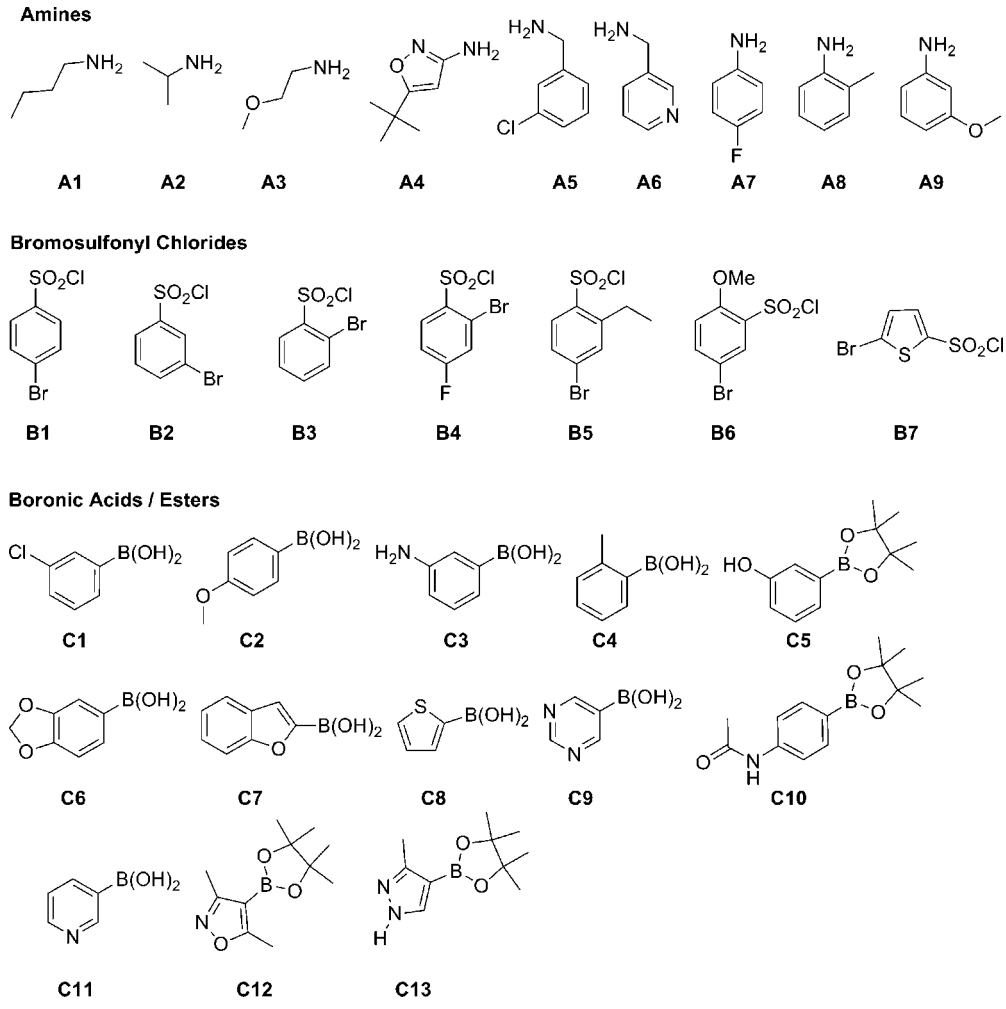


Figure 2. Library monomers.

Table 2. LC-MS Analysis of the Library (52 Randomly Selected Compounds)

purity	number of compounds
>95%	21
90–94%	18
80–89%	3
70–79%	3
60–69%	1
<60%	6

The resin-bound amines were distributed into the appropriate Kans (0.025 g/Kan), already containing a radiofrequency tag, via an isopycnic solution of DCM/hexane. In brief, the resin was placed in a 100 mL graduated cylinder, and the cylinder was filled with 40 mL of hexane. DCM was added until an isopycnic mixture was formed. The total volume was divided by the number of Kans required (i.e., 91 for each amine); this amount of the solution was then allocated to each Kan. The Kans were then capped and washed with cycle A.

The resin-filled Kans were desiccated over silica gel prior to use in each reaction.

During each reaction, a vacuum (water aspirator) would periodically (at least 3 times per reaction cycle) be applied to the reaction vessel for approximately 1 min and then backfilled with argon. This was done to force the solvents and reagents to flow out of and then back into the Kans.

Tracking of the Kans during the library synthesis was done according to the manufacturer's guidelines.

Step 1: Attachment of Amines. 4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin **3** (2.45 g, 4.1 mmol, 1.54 or 1.64 mmol/g loading) (supplied by Novabiochem or Advanced ChemTech) was placed in a 40 mL fritted syringe tube and desiccated over P_2O_5 and KOH prior to use.

To the resin was added DCM (20 mL), and the slurry was agitated for 5 min before the addition of the amine (4.5 mmol) and a further 10 min of agitation. To the slurry was added $TiCl(O^iPr)_3$ (2.4 mL, 10 mmol), and the reaction mixture was shaken for 10 min before the addition of freshly ground $NaBH(OAc)_3$ (4.26 g, 20.1 mmol) and AcOH (5 drops). [***Caution****! This causes an exotherm and the evolution of gas.*] The suspension was then agitated for 24 h before filtering and washing with cycle B. The amounts of amines were as follows: propan-2-amine, 0.376 mL; 2-methoxyethanamine, 0.395 mL; 5-*tert*-butylisoxazol-3-amine, 0.620 g; (3-chlorophenyl)methanamine, 0.540 mL; 4-fluoroaniline, 0.419 mL; *o*-toluidine, 0.472 mL; pyridin-3-ylmethanamine, 0.450 mL; and 3-methoxyaniline, 0.497 mL.

Attachment of *n*-Butylamine. To the resin-filled syringe tube was added DMF (15 mL)/AcOH (0.15 mL), and the reaction mixture was agitated for 15 min, before the addition of *n*-butylamine (1.99 mL, 20 mmol); then, there was a further 30 min of agitation. Freshly ground $NaBH(OAc)_3$ (4.26 g, 20.1 mmol) was added, followed by DMF (5 mL) to increase the fluidity of the slurry. The vessel was then agitated for 16 h before filtering and washing with cycle B.

Step 2: Sulfonylation. To the dried and sorted Kans (117 Kans per sulfonyl chloride, 3.15 g resin, 5.2 mmol) in a 250 mL round-bottom flask was added $CHCl_3$ (100 mL), pyridine (25 mL), and DMAP (0.928 g, 10.4 mmol). The reaction mixture was then gently stirred for 10 min before the addition of the sulfonyl chloride (25 mmol, 5 equiv). The resulting mixture was then gently stirred at 40 °C for 48 h. The Kans were then washed, (cycle C) dried, and resubjected to the sulfonylation conditions. The amounts of sulfonyl chlorides were as follows: 4-bromobenzene-1-sulfonyl chloride, 6.56 g; 3-bromobenzene-1-sulfonyl chloride, 6.56 g; 2-bromobenzene-1-sulfonyl chloride, 6.56 g; 2-bromo-4-fluorobenzene-1-sulfonyl chloride, 7.07 g; 4-bromo-2-ethylbenzene-1-sulfonyl chloride, 7.32 g; 5-bromo-2-methoxybenzene-1-sulfonyl chloride, 7.34 g; 5-bromothiophene-2-sulfonyl chloride, 6.76 g.

Step 3: Suzuki Cross-coupling. To the dried and sorted Kans (63 Kans per boronic acid/ester, 1.58 g resin, 2.6 mmol) in a 250 mL round-bottom flask was added DME (63 mL) and aqueous Na_2CO_3 (4 mL of 2 N, 8 mmol). The reaction mixture was then gently stirred for 10 min before the addition of the boronic acid (39 mmol) and $PdCl_2$(dppf) (1.06 g, 0.26 mmol, 0.1 equiv). The mixture was then gently stirred at 100 °C for 48 h before filtering and washing (cycle C). The amounts of boronic acids were as follows: 3-chlorophenylboronic acid, 6.06 g; 4-methoxyphenylboronic acid, 5.89 g; 3-aminophenylboronic acid, 6.01 g; *o*-tolylboronic acid, 5.27 g; 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, 5.34 g; benzo[*d*][1,3]dioxol-5-ylboronic acid, 6.43 g; benzofuran-2-ylboronic acid, 6.28 g; thiophen-2-ylboronic acid, 4.96 g; pyrimidin-5-ylboronic acid (85% purity, 5.67 g); *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide, 10.12 g; pyridin-3-ylboronic acid, 4.76 g; 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole, 8.64 g; 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1 *H*-pyrazole (50% purity); 16.12 g.

Step 4: Cleavage. After the Kans were sorted into a Bohdan Mini-block (2 × 48 position arrays of fritted syringe tubes cleaved into a single 96-well plate), each Kan was decapped and the resin was transferred to the fritted syringe tube. The loose resin was then washed (cycle D) and filtered. The loose resin was then agitated with 50:50:1 TFA:DCM:H_2O (0.2 mL) for 2 h at room temperature and filtered into a 96-well plate (2.2 mL deep wells). The loose resin was then washed with MeOH (0.2 mL) and filtered into the 96-well plate. A second treatment with 50:50:1 TFA:DCM:H_2O (0.2 mL) for 2 h was performed followed by washing with MeOH (0.2 mL) and DCM (0.2 mL) (2 times with each solvent); all solvents were filtered into the 96-well plate. The solvents were then removed in a Genevac, and the products were desiccated over silica gel and KOH.

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Supporting Information Available. Experimental procedures, synthesis of monomers, and ^1H NMR spectra of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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